Formulation of Brinzolamide Nanolipid Carrier-Based Ocular Gel System Co-loaded with Antioxidant Bioactive Compounds for Management of Glaucoma

Synopsis

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Introduction

Glaucoma is a serious eye disorder characterized by an increase in intraocular pressure, which leads gradually to loss of vision due to damage of the optic nerve with no symptoms. Glaucoma is the second most common cause of blindness worldwide. In India, glaucoma is the leading cause of irreversible blindness with at least 12 million people affected and nearly 1.2 million people blind from the disease. Medication requires frequent administration daily of single or combination of drugs like beta-blockers (betaxolol, timolol, carteolol), cholinergic agonists (pilocarpine, aceclidine, carbachol), α2-agonists (apraclonidine, brimonidine), carbonic anhydrase inhibitors (brinzolamide, dorzolamide), etc. Amongst them, brinzolamide, a non-competitive, reversible and effective inhibitor of carbonic anhydrase II plays an important role in glaucoma treatment. Azopt® (Alcon Laboratories, USA) is a commercially available aqueous multiple use sterile ophthalmic suspension of 1% w/v of brinzolamide. It showed rapid elimination from the precorneal space upon instillation due to physiological constraints imposed by the protective mechanism of the eye like tear turnover and nasolacrimal drainage, limiting intraocular bioavailability of the drug to less than 10% of the administered dose. The incorporation of ophthalmic drugs in nanocarriers has gained interest due to its potential to prolong ocular residence and sustain drug release. Furthermore, nanocarriers do not alter transparency or the desirable ophthalmic characteristics like the case with suspensions or ointments. Nanolipid carrier-based ocular gel system are appealing for controlled and extended delivery of hydrophobic drugs like brinzolamide.

Literature Review

Different bioflavonoids like quercetin, rutin, and curcumin possess antioxidant and anti-inflammation properties. Previous clinical and experimental studies have reported that oxidative stress and inflammation associated with trabecular meshwork cell dysfunction increase the aqueous outflow resistance (Tanito *et al*., 2015). In a study, combination of antiglaucoma drug latanoprost with curcumin has been reported and shows greater potential towards the effective treatment of glaucoma. The results suggest that a combination of curcumin might enhance trabecular meshwork outflow and is promising to develop into a novel treatment for glaucoma. **(**Cheng *et al.,* 2019).

In another study the combination of resveratrol and quercetin produce the synergistic

effect and enhanced the reduction of intraocular pressure (5.5±0.5 mmHg) in normotensive rabbits (Netasan et al. 2017).

Gaps in literature

In recent years, few novel formulation approaches have been investigated for ophthalmic delivery of brinzolamide. These include nanocrystals, β-cyclodextrin complexation, nanoemulsions formulation and *in situ* gelling formulation to increase ocular residence time, drug penetration across the ocular barriers and ophthalmic bioavailability. They showed prolonged intraocular pressure (IOP) lowering ability for the duration of 6-8 h. There is a need for long-acting formulation of brinzolamide with prolonged intraocular pressure (IOP) lowering effect lasting for 16–24 h so, that the dosing frequency can be drastically reduced. The development of Brinzolamide (BZ) loaded nanostructured lipid carrier (NLC) based gel formulation and its combination with bioactive compounds like curcumin, quercetin, resveratrol and rutin have not been attempted before.

Rationale and Justification

Brinzolamide 1% suspension (Azopt, Alcon Laboratories) has been prescribed three times a day in open-angle glaucoma and ocular hypertension. Unfortunately, this formulation is associated with several side effects, such as blurred vision, pain, discomfort (stinging and burning), eye discharge, blepharitis, dry eye, taste perversion, poor aqueous solubility, granular sensation, and multiple dosing requirement (3 times/day). To overcome the drawbacks of conventional eye drops, NLC based hydrogel will be designed. BZ loaded NLC could promote the pre-corneal residence time and corneal absorption through the ocular tissues due to their nanoscale dimensions while BZ-NLC loaded hydrogel would provide sustained release effect by increasing the viscosity of NLC.

Despite potency BZ, long-term application of it may cause undesirable side effects and many require adjunctive therapy to control their IOP, the combination product therapy would fare better than one component. Recent studies have suggested that oxidative stress in the trabecular meshwork play an important role in the pathogenesis of impaired trabecular outflow facility. Different bioflavonoids like quercetin, rutin, resveratrol, and curcumin possess antioxidant and anti- inflammation properties. Therefore, BZ in combination with bioflavonoids might improve trabecular meshwork outflow and help to improve its efficacy in addition to its antioxidant activity. Therefore, our aim is to formulate nanocomposite hydrogel consisting of bioactive agents with brinzolamide for effective management of glaucoma.

Objectives

- Formulation and optimization of BZ-NLC and its combination with bioactive compounds like quercetin, curcumin, resveratrol and rutin.
- Incorporation of optimized NLCs in hydrogel and its evaluation.
- Comparative evaluation of optimized BZ-NLC-HG, BZ-NLC-HG with bioactive compounds and marketed brinzolamide eye drops for antiglaucoma efficacy.

Plan of Work

- To develop and evaluate Nanolipid Carrier-Based Ocular Gel System brinzolamide along with bioactive compounds for the potential application in glaucoma therapy.
- Optimization and Characterization of prepared Nanolipid Carrier-Based Ocular Gel System.
- To determine the *in vitro* and *in vivo* activity of Nanolipid Carrier-Based Ocular Gel System

Methodology

- Characterization of drug (IR spectroscopy, UV, DSC, FTIR etc.)
  Analytical method development (UV spectrophotometry)
- Preformulation studies (solubility, partition coefficient and drug excipients Compatibility)
- Preparation and optimization of brinzolamide NLC (Melt- emulsification combined with ultra-sonication technique)
- Characterization of drug NLC (Particle size, zeta potential, PDI, and entrapment efficiency)
- Preparation and optimization of Hydrogel and Characterization of Gel (Zeta potential, viscosity, pH, gelling time, rheology, osmolarity etc.)
- Preparation NLC loaded hydrogel (Swelling and loading method.)
- *In vitro* release studies (Dialysis bag technique/ Franz diffusion.)
- *In vitro* trans-corneal permeation studies (Franz diffusion using goat cornea.)
- DPPH antioxidant assay
- Ocular tolerance test (HET-CAM, In vivo ocular irritancy test).
- Comparative IOP study with reduced dose and marketed formulations.
- Comparative IOP study of NLC loaded gel of BZ and co-loaded with bioactives.

Expected Outcomes

- Developed nanocomposite-hydrogel delivery system can achieve prolonged therapeutic action over an extended period with a single dose of brinzolamide.
- Developed nanocomposite-hydrogel delivery system can produce a desirable therapeutic effect with lower concentrations of BZ, hence reduced dose burden and lower side effects.
- Combination of BZ with bioactive compounds like curcumin, quercetin, resveratrol, and rutin, can improve IOP lowering efficacy as compared with monotherapy of BZ.

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